REMARKS

Claims 164, 177, 307-328 are pending. In addition, the Examiner has withdrawn Claims 312-315 and 324-328 as being drawn to a non-elected invention. Therefore, Claims 164, 177, 307-311 and 317-323 are under examination. No claim amendments have been made in response to this current Office action.

Withdrawn Rejections

The Examiner has withdrawn the rejection of Claims 164, 310 and 317-318 under 35 U.S.C. §102(b) as being anticipated by Doyen et al., (herein referred to as "Doyen") (*Mol. Immunol.*, volume 22, pages 1-20 (1985)) as evidenced by Glowacki et al. (herein referred to as "Glowacki") *(J. Biol. Chem.*, volume 279, pages 10864-10871 (2004) in view of the previously presented claim amendments and remarks.

The Examiner has withdrawn the rejection of Claims 164, 177, 307-310, and 317-322 under 35 U.S.C. 103(a) as being unpatentable over Doyen et al., in view of U.S. Patent No. 5,198,340 and as evidenced by Glowacki et al., in view of the previously presented claim amendments and remarks.

The Examiner has withdrawn the rejection of Claims 311 and 323 under 35 U.S.C. 103(a) as being unpatentable over Doyen et al., in view of Gavilondo et al., (2000, *Biotech*, Vol 29: 128-145), as evidenced by Glowacki et al., in view of the previously presented claim amendments and remarks.

Rejection Under 35 U.S.C § 103(a) - Peters in view of US Patent 5,223,392 and US Publication No. 2003/0124616

The Examiner has rejected Claims 164, 177, 307-311, 317-323 under 35 U.S.C. 103(a) as being unpatentable over Peters 1995 (herein referred to as "Peters") in view of US Patent 5,223,392 (herein referred to as '392) and US Publication No. 2003/0124616 (herein referred to as '616).

Specifically, the Examiner asserts that Peters teaches that human albumin exists as several modified forms in the blood, including a form comprising disulfide-bound cysteine at an unpaired cysteine at position 34 and that various techniques can be used to determine the sulfhydryl content of albumin. The Examiner notes that Peters does not teach an antibody specific to the cysteinylated form of albumin. Therefore, the Examiner cites '392 as teaching the production of antibodies specific for a modified form of albumin and asserts that these antibodies are capable of distinguishing modified and unmodified albumin and that '392 teaches that monoclonal antibodies, or antibody fragments, are suitable for measuring modified albumin. The Examiner also asserts that '616 teaches detecting homocysteinylated proteins, including homocysteinylated albumin, with an antibody that specifically binds to said homocysteinylated proteins.

The Examiner bears the burden of establishing a *prima facie* case of obviousness (MPEP § 2142). The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious (MPEP § 2142). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007), noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). Applicants respectfully traverse the rejection based on this combination of references as these references, individually, and as a whole, do not provide one of skill in the art with a rational reason to prepare the antibodies of the currently pending claims or any expectation or guidance for successfully doing so.

Specifically, none of the cited references, either alone or in combination, teach or suggest the antibodies of the present invention. The pending claims require an isolated antibody that selectively binds to a cysteinylated albumin protein wherein the antibody does not detectably bind to the albumin protein in the absence of cysteinylation. As previously discussed, cysteinylated albumin has a disulfide-bonded cysteine residue at amino acid residue 34, whereas non-cysteinylated albumin does not contain this disulfide bonded cysteine. Applicants previously argued that an antibody directed toward non-cysteinylated albumin may not bind cysteinylated albumin, as such antibodies may specifically recognize and bind to an epitope including Cys 34 that is not cysteinylated. Conversely, an antibody directed toward cysteinylated albumin may not bind to non-cysteinylated albumin. As such, antibodies may specifically recognize and bind to an epitope including Cys 34 that includes an additional cysteine residue through a disulfide bond.

With respect to the teachings of Peters, and as stated by the Examiner, Peters does not teach or suggest an antibody that can distinguish between the cysteinylated and the non-cysteinylated forms of albumin. Rather, Peters merely teaches that such cysteinylated forms of albumin exist.

The Examiner states that the ‘392 patent teaches the production of antibodies specific for a modified form of albumin. The modification taught is a glycated form of albumin, and the ‘392 patent specifically teaches antibodies that recognize a glycated albumin and can distinguish between glycated albumin and unglycated albumin (‘392 patent at column 7 lines 3-9). There is no mention or recognition of cysteinylated forms of albumin or methods of distinguishing between cysteinylated and non-cysteinylated forms. Additionally, there is no teaching or guidance for the production of antibodies that selectively bind to a cysteinylated albumin protein and do not detectably bind albumin protein in the absence of cysteinylation. It is known by those of skill in the art that glycation has the potential to alter the biological structure and function of the albumin protein. Additionally, different amino acids take part in the glycation reaction (a few lysine and arginine residues), than those cysteine residues that are cysteinylated in the albumin protein. Therefore, there would be no expectation that an antibody that distinguishes between glycated and un-glycated albumin would be similar to, or share the epitope of, an antibody that distinguishes between cysteinylated and non-cysteinylated albumin.

The Examiner correctly states that the '616 patent mentions a homocysteinylated albumin protein. As noted previously with respect to the'616 publication, a cysteinylated albumin protein is not a homocysteinylated albumin protein. Further, the '616 publication only discloses antibodies that detect the presence of **homocysteinylated transthyretin** (see, for example, paragraph [0043] of the '616 publication). The '616 application only speculates that **homocysteinylated** albumin may be used in place of homocysteinylaed transthyretein in an immunoassay (see, for instance, paragraphs [0006] and [0008]), and an antibody to a cysteinylated albumin protein is never described, nor suggested, and no guidance is provided for preparing or isolating an antibody specific to a cysteinylated albumin. Accordingly, the '616 publication provides no teaching or suggestion to one of skill in the art for preparing or identifying an antibody that specifically binds to a cysteinylated albumin protein, nor provides any suggested uses or other motivations to try and prepare such antibodies of the presently-pending claims.

In citing this combination of references, the Examiner states that Peters teaches one of skill in the art that cysteinylated forms of albumin exist and the '392 patent shows that antibodies have been made that distinguish between glycated forms of albumin. Therefore, the Examiner argues that one of skill would make and use the antibodies of the present invention, that can selectively bind cysteinylated albumin and not detectably bind albumin in the absence of cysteinylation, in order to have an accurate and specific means of measuring cysteinylated albumin in the blood and to avoid the problems of reproducibility, cost, expense, instrumentation, and accuracy involved with other methods of measuring modified forms of albumin.

As described above, however, the Peters, the '392 patent, or the '616 publication, do not teach any antibodies, expressly or inherently, that selectively bind a cysteinylated albumin protein and do not detectably bind a non-cysteinylated albumin. Additionally, the Peters, the '392 patent, or the '616 publication, individually and collectively, do not provide any guidance to one of skill in the art to make and use such antibodies, for any purposes. The Examiner's rejection appears to be premised on the argument that Peters acknowledges the existence of cysteinylated albumin, while the ‘392 patent and the ‘616 publication teach the production of antibodies to other protein modifications, and one of skill in the art would therefore find it obvious to make and use antibodies that selectively bind cysteinylated albumin. But Applicants submit that, lacking any guidance in how to make and use such antibodies, one of skill in the art would not find it obvious to do so, and would not have any expectation of successfully doing so simply because Peters discloses the existence of cysteinylated albumin and ‘392 patent and the ‘616 publication teach the production of antibodies with different specificities. Additionally, as the Peters, ‘392 patent, and ‘616 publication do not teach any antibodies that selectively bind cysteinylated albumin, there is no indication that such antibodies could “avoid the problems of reproducibility, cost, expense, instrumentation, and accuracy” or that these problems currently exist with any means of detecting cysteinylated albumin.

In view of the foregoing, it is respectfully submitted that Claims 164, 177, 307-311, 317-323, and claims depending therefrom, are allowable and Applicants respectfully request withdrawal of the rejection based on the combination of Peters, the ‘392 patent, and the ‘616 publication.

Conclusion

Applicants submit that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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